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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,173	08/31/2001	Rachel Meyers	381552003500	3164

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MILLENNIUM PHARMACEUTICALS, INC.
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CAMBRIDGE, MA 02139

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,173	MEYERS, RACHEL	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,26-28,30,31,33,35,36,38 and 40-42* is/are rejected.

7)☒ Claim(s) *2,25,29,32,34,37 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 4/11/2005. The amendment filed 4/1/0225 is acknowledged. The amendment has been entered. Claims 1-3, 6, 25-42 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/11/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

Claims 1, 3, 6, 26-28, 30, 31, 33, 35, 36, 38 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for An isolated 47324 nucleic acid molecule selected from a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1; and b) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3, as well as a vector comprising said isolated nucleotide sequence(s) and an isolated host cell comprising said isolated nucleotide sequences;

does not reasonably provide enablement for the full scope of the instant claims. Specifically, the instant claims are not enabled for any nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, a host cell comprising any nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, or a method of producing said amino acid sequence, for the reasons of record which are reiterated below for convenience. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to an isolated 47324 nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO: 2, which includes the nucleic acid sequences that are SEQ ID NO: 1 (a full length cDNA encoding SEQ ID NO: 2, including untranslated regions) and SEQ ID NO: 3 (only the coding sequence of the cDNA encoding SEQ ID NO: 2), as well as a vector comprising said sequence(s), an isolated host cell comprising said nucleic acid sequence(s) and methods for making the polypeptide that is SEQ ID NO:2 using the nucleic acid(s)/cell.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The broad claims encompass any isolated nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 2, as well as a vector comprising said nucleic acid sequence, an isolated host cell comprising said nucleic acid sequence, and methods of making the polypeptide using the nucleic acids/cell.

Working Examples and Guidance in the Specification

The instant application discloses that the mRNA corresponding to SEQ ID NO: 1 exhibits altered expression in certain cell types. For instance, real-time PCR was used to identify that the mRNA corresponding to SEQ ID NO: 1 was significantly overexpressed in lung tumor cells compared to normal lung cells, as well as in prostate cancer cells compared to normal prostate cancer cells, etc. (e.g., the specification discloses the expression levels of SEQ ID NO: 1 mRNA in a plethora of cell types, some of which show altered expression of SEQ ID NO: 1 mRNA). It is noted that the real-time PCR is only indicative of the mRNA levels, and not necessarily indicative of the level of protein encoded by the mRNA. As such, the disclosure indicates utility for the claimed nucleic acids. However, regarding enablement, the specification only provides enablement for the isolated nucleic acid sequences comprising SEQ ID NO: 1 and 3 (and vectors and isolated cells comprising said nucleic acids) for their use in diagnosing specific cancers (such as lung cancer and prostate cancer, as indicated above). It is noted that there is no disclosure indicating that any sequence other than SEQ ID NO: 1 (such as a variant of SEQ ISD

NO: 1) is overexpressed in the cancerous cells. Additionally, there is no disclosure provided which indicates that the protein levels (of SEQ ID NO: 2) are commensurate with the corresponding mRNA levels, which would be required in order for the protein levels to be diagnostic indicators of cancer, etc. Furthermore there is no specific activity/function disclosed for the amino acid sequence of SEQ ID NO: 2.

The unpredictability of the art and the state of the prior art

The relevant art indicates that nucleic acid expression is not necessarily indicative of the level of the encoded protein in a cell. For instance, Meric et al. (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

Additionally, with respect to the expression of Endothelial Differentiation Gene (Edg) encoded G protein-coupled Receptors, Goetzl et al. (Cancer Research (1999) 59:5370-5375) teaches that the expression of Edg mRNA is not always indicative of the Edg protein level in the cell. Specifically, when analyzing Edg-2 and Edg-5 mRNA levels (by semiquantative RT-PCR) and protein levels (by Western blot) in normal ovarian samples (IOSE) and ovarian cancer samples (OV202), the level of Edg-2 mRNA did not appear significantly different in the samples in IOSA samples than OV202 samples. However, Edg-2 protein levels were significantly higher in the IOSA samples than the OV202 samples (e.g., see Figure 1, Figure 2, Table 1; as well as the paragraph bridging pages 5371-5372). Therefore, the mRNA level of GPCRs are not always indicative of the corresponding protein level in the cell.

It is noted that Schrader et al. (Journal of Urology, 2003; Vol. 169, pages 1858-1864) reviews the state of the art of real-time PCR and indicates that real-time PCR can be used to accurately assay the mRNA levels in a sample. Specifically, Schrader teaches, "Real-time RT-PCR is a reliable, rapid and relatively inexpensive technique that can be easily adapted for standardized preclinical and clinical applications at different centers." (See abstract). However, Schrader does not address the issue of correlating the mRNA level to the corresponding protein levels in a cell. As such, Schrader indicates the utility of real-time RT-PCR as a diagnostic indicator of mRNA levels, but does not overcome the problems recognized in the art with respect to using mRNA levels as indicators of protein levels in a sample.

With respect to any nucleic acid encoding SEQ ID NO:2, it is noted that the claims encompass sequences which are different from SEQ ID NO:1 and 3, but which still encode SEQ ID NO:2. Since the specification has disclosed that the nucleic acid of SEQ ID NO:1 and 3 can

be used in diagnostic assays to identify the level of 47324 mRNA in a cell, which has been disclosed as altered in certain cell types (e.g., lung tumor cells, prostate tumor cells, liver fibrosis cells, etc.), the specification is enabling only for using sequences of SEQ ID NO:1 and 3 to assay mRNA level. However, a nucleic acid sequence which encodes SEQ ID NO: 2 encompasses nucleic acid sequences which are significantly different from SEQ ID NO:1 and 3 (based on the wobble hypothesis). The nucleic acids encompassed by the claims which are different from SEQ ID NO: 1 and 3 would encompass sequences which would not specifically hybridize to the target mRNA. As such, nucleic acid sequences encoding SEQ ID NO: 2 would not be useful in methods of determining mRNA levels in a cell. Therefore, the claims are not enabled for any nucleic acid sequence other than nucleic acids sequences comprising SEQ ID NO:1 and SEQ ID NO: 3.

Quantity of Experimentation

In view of the breadth of the claims and the unpredictable nature of the invention, as recognized in the art (see above) additional experimentation would have to be performed in order to make and use the claimed invention. Considering that mRNA levels are not indicative of protein levels, additional experimentation would be required in order to determine that mRNA levels are commensurate with protein levels.

Level of the skill in the art

The level of the skill in the art required for biotechnology applications is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the limited amount of working examples and guidance provided in the specification, as well as the teachings of the relevant art and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention to its full scope is undue.

Response to Arguments

Applicant's arguments filed 4/11/2005 have been fully considered. With respect to the rejection of claims under 35 USC 112, 2nd paragraph, Applicants' arguments, in view of the amendment to the claims, are persuasive and the rejection is withdrawn. With respect to the objection of claims 21-31, Applicants' arguments, in view of the amendment to the claims, are persuasive and the objection to claims 21-31 is withdrawn.

With respect to the rejection of claims under 35 USC 112, 1st paragraph, Applicants arguments have been fully considered but they are not fully persuasive. Specifically, the amendment limiting the claims to an isolated host cell is sufficient to overcome the rejection as it pertains to a non-isolated host cells. However, Applicants' arguments are not sufficient to overcome the rejection as it pertains to isolated nucleic acid sequences which encode the amino acid sequence of SEQ ID NO: 2 other than SEQ ID NO: 1 or SEQ ID NO: 3 or for the methods of making a polypeptide.

Applicants argue that the specification is enabling for any nucleic acid sequence encoding SEQ ID NO: 2. The Applicants argue that the exact amino acid sequence to be encoded by the claimed nucleic acid sequences is set forth in SEQ ID NO: 2 and that the requisite knowledge to determine the number and nucleotide sequence of any possible nucleic acid sequence encoding

the polypeptide of SEQ ID NO: 2 existed and was well-known in the art at the time of filing. Applicants further submit that the number of nucleotide sequences encoding SEQ ID NO:2 is finite and not unlimited and starting with the amino acid sequence of SEQ ID NO:2, one of skill in the art could use this information to precisely determine the exact nucleotide sequence of any and every nucleic acid encoding SEQ ID NO:2. Applicants also submit that the claims do not require knowledge of any definitive necessary correlation between mRNA and protein levels and assert that even if the arguments are true in some in vivo situations, such assessment is not relevant to the presently claimed subject matter relating to isolated nucleic acids, host cells, and methods of producing polypeptides. Thus, Applicants contend, one of ordinary skill in the art, given the sequences set forth in the instant sequence listing, the teachings provided in the specification, and information well-known in the art at or before the time of filing, would very predictably be able to practice the claimed invention without undue experimentation. (See pages 5-7 of the response filed 4/11/2005).

In response Applicants arguments have been fully considered, but they are not persuasive.

First, the Examiner would like to clarify the rejection in order to clearly convey why the specification provides an enabling disclosure only for the nucleic acid sequences disclosed as SEQ ID NO: 1 and SEQ ID NO: 3, but not for any nucleic acid sequence encoding the polypeptide of SEQ ID NO: 2.

As indicated above, the specification has disclosed that the nucleic acid sequence of SEQ ID NO: 1 (which comprises the sequence of SEQ ID NO: 3) is found at significantly elevated levels in specific cancers, as determined by real-time PCR, which is sufficient to provide

enabling disclosure for SEQ ID NO: 1 or SEQ ID NO: 3 for their use in identifying specific cancer cells. Therefore, the specification has provided an enabling disclosure for the isolated nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 3, a vector comprising the nucleic acid sequence, and an isolated host cell comprising said nucleic acid sequences as the nucleic acid sequences of SEQ ID NO: 1 and SEQ ID NO: 3 are enabled for identifying specific cancer cells and the vector and isolated host cells are enabled for making said nucleic acid sequences. The specification, however, does not provide an enabling disclosure for any nucleic acid sequence that encodes the polypeptide of SEQ ID NO: 2 (other than SEQ ID NO: 1 and 3) or a method of making said polypeptide because (1) the specification does not provide an enabling disclosure for the polypeptide of SEQ ID NO:2; (2) there is no indication that any sequence other than SEQ ID NO: 1 (which comprises SEQ ID NO: 3), such as a degenerate variant of SEQ ID NO: 1, is overexpressed in the cancer cells; and, (3) the nucleic acids which are different from SEQ ID NO: 1 and 3 but which encode the polypeptide of SEQ ID NO: 2 include sequences that would not specifically hybridize to the target mRNA sequence (SEQ ID NO: 1).

It is noted that the claims encompass any nucleic acid sequence which encodes the polypeptide of SEQ ID NO: 2 including nucleic acid sequences that are significantly different from SEQ ID NO:1 and 3 and which would not specifically hybridize to the target mRNA. The nucleic acid sequences which do not specifically hybridize to the target mRNA sequence would not be useful in methods of determining mRNA levels in a cell. Therefore, the claims are not enabled for any nucleic acid sequence other than nucleic acids sequences comprising SEQ ID NO:1 and SEQ ID NO: 3.

There is no indication that the polypeptide encoded by SEQ ID NO: 1 and SEQ ID NO: 3 is overexpressed in the cancer cells. Furthermore, the prior art of record teaches that the amount of a nucleic acid in a cell is not necessarily indicative of the amount of the polypeptide encoded by the nucleic acid in the cell (e.g., see Meric et al., Gokman-Polar, and Goetzl et al.). Therefore, the specification has not provided an enabling disclosure for the polypeptide of SEQ ID NO: 2. Since the specification has not provided an enabling disclosure for the polypeptide of SEQ ID NO: 2, the specification also fails to provide an enabling disclosure for any nucleic acid sequence encoding the polypeptide of SEQ ID NO: 2 or for a method of making the polypeptide of SEQ ID NO: 2 using the isolated nucleic acid sequences, vectors, and isolated host cells.

With respect to Applicants' arguments that the exact amino acid sequence to be encoded by the claimed nucleic acid sequences is set forth in SEQ ID NO: 2 and that the requisite knowledge to determine the number and nucleotide sequence of any possible nucleic acid sequence encoding the polypeptide of SEQ ID NO: 2 existed and was well-known in the art at the time of filing. It is acknowledged that the specification discloses that the exact sequence of SEQ ID NO: 2 has been disclosed and that the means for determining all of sequences encoding SEQ ID NO: 2 were known in the art. Therefore, it is acknowledged that the sequences encompassed by the claims could be made without undue experimentation. However, at issue is whether or not the specification has provided an enabling disclosure sufficient to teach on of skill in the art how to use the claimed sequences. Since the specification does not provide an enabling disclosure for the polypeptide of SEQ ID NO: 2 for the reasons indicated above, the specification also fails to provide an enabling disclosure for methods of making the polypeptide of SEQ ID NO: 2. Furthermore, since the claims encompass any nucleic acid sequence that encodes the

polypeptide of SEQ ID NO: 2 including variants of SEQ ID NO: 1 and 3 which are significantly different from SEQ ID NO:1 and 3 and which would not specifically hybridize to the sequence o of SEQ ID NO: 1 or 3. It is also noted that SEQ ID NO: 1 is nearly 1700 nucleotides long. Considering the degeneracy of the genetic code, and specifically that each amino acid might have up to six different codons that specify it, the claims encompass an enormous number of different sequences.

With respect to Applicants' arguments that that the claims do not require knowledge of any definitive necessary correlation between mRNA and protein levels and assert that even if the arguments are true in some in vivo situations, such assessment is not relevant to the presently claimed subject matter, the argument has been fully considered, but is not persuasive. It is respectfully pointed out that in order for the method of making a polypeptide to be enabled, the polypeptide itself must be enabled. In the instant case, the specification does not provide an enabling disclosure for the polypeptide of SEQ ID NO: 2 for the reasons indicated above. Therefore, the nucleic acid sequences which encode the polypeptide of SEQ ID NO: 2, are not enabled for use in making the polypeptide of SEQ ID NO: 2. Furthermore, considering the enormous number of different sequences which are encompassed by the claims, which includes sequences which would not specifically hybridize to SEQ ID NO: 1, and further considering that there is no indication that any variants of SEQ ID NO: 1 are significantly overexpressed in cancer cells; the specification does not provide an enabling disclosure for the sequences encompassed by the claims other than the nucleotide sequences of SEQ ID NO: 1 and SEQ ID NO: 3. Since the specification has not provided an enabling disclosure for the polypeptide of SEQ ID NO: 2 or for the nucleic acid sequences which encode the polypeptide of SEQ ID NO: 1

or SEQ ID NO: 3, one of skill in the art would not know how to use the claimed invention to its full scope without performing an undue amount of additional experimentation.

It is noted that limiting the claims to an isolated nucleic acid encoding SEQ ID NO:1, SEQ ID NO:3 well as vectors and isolated host cells comprising SEQ ID NO: 1 or SEQ ID NO: 3 would obviate this rejection.

Allowable Subject Matter

Claims 2, 25, 29, 32, 34, 37 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER